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Short communication

Aniline-initiated and BrØnsted acid-catalyzed one-pot reaction toward 2-aryl-3-sulfenylindoles by using α-aminocarbonyl compounds and primary amines with RSSR

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ABSTRACT

A highly novel method of direct synthesis of 2-aryl-3-sulfenylindoles in moderate to good yields was developed via one-pot tandem reaction of readily available α-aminocarbonyl compounds and catalytic amount of benzenamines with RSSR.

1. Introduction

Indole frameworks are known to be widely distributed in diverse pharmacophores and natural products. Among these, 3-sulfenylindoles are reported to display important biological activities in the treatment of cancer, HIV, obesity, allergy, and many common diseases [1–5].

In the past few decades, continuous efforts have been made to search for efficient methods for the construction of 3-sulfenylindoles [6–9]. The vast majority of reported transformations are the direct sulfenylation [10–18] of indoles with disulfide [19], thiol [20–21], N-thioalkyl (aryl) -phthalimide [22], S-acetaldehyde [23], quinone mono [24], direct sulfide of thiocyanate or ammonium thiocyanate [25–26], and benzenesulfonyl hydrazide [27]. In 2009, Guo (Scheme 1a) reported a novel and attractive method to construct 3-sulfenylindoles in 92% yields using 2-aminobiphenylacetylene and phenyl sulfide with Palladium catalyst [28]. However, we also expect a metal-free and efficient method to obtain such compounds. According to the study of Janakiram Vaitla's group for the synthesis of indoles (Scheme 1b) [29] and the experimental research of the previous work (Scheme 1c) [30], we assumed that the two experiments could be combined to develop a novel one-pot method to synthesize 3-sulfenylindoles, and thus, we performed a detailed study (Scheme 1d).

2. Result and discussion

Inspired by these, we envisioned that a free radical reaction of sulfide and indole which could be generated in situ from α-aminoacet-ophenone and catalytic amount of aniline might give an approach to the construction of target 3-sulfenylindole.

frameworks. Initially, we commenced our study using α-aminoacetophenone (1 equiv) and a catalytic amount of aniline (0.3 equiv) as the model substrate. Screening of acid catalyst, solvent, and temperature is shown in the supporting information (Table S1). Under the optimal reaction condition, we added phenyl disulfide and iodine into the system to explore the possibility of novel one-pot reaction that we mentioned above. Interestingly, the desired product was obtained while the yield was only 32%. Thus, we tested various non-metallic catalysts to promote this transformation, as shown in Table 1 for acid catalyst, $LiClO_4$, PPA, and acetic acid had no positive effect in this transformation, while trifluoromethanesulfonic acid and p-toluenesulfonic acid greatly improved the yield. We chose TfOH as the best catalyst. Then, we studied the effect of the reaction solvent. We initially believed that the second step of this reaction was a free radical reaction, so we chose toluene, trifluorotoluene, and dichloroethane as the reaction solvent. Examination of several solvents (entries 7–12) at the same temperature revealed that DCE might be the better solvent [31–33]. Additionally, further studies on increasing or decreasing temperature and reaction time of two steps did not show any superior result.

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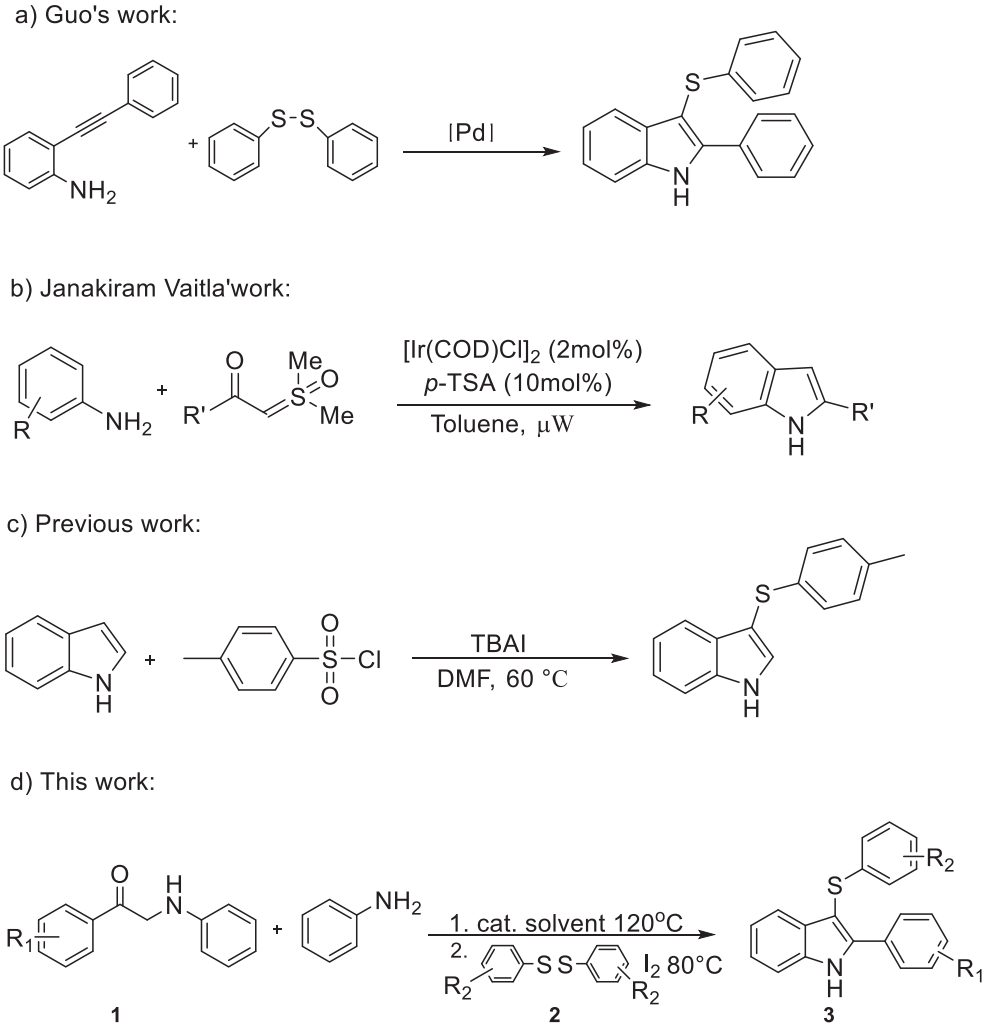
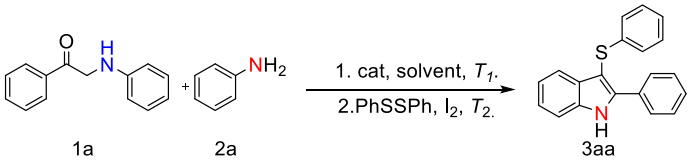


Scheme 1. Various approaches for the synthesis of indoles.

Table 1
Optimization of the reaction conditions.[a]



1a 2a 3aa

Entry	Catalyst (x mol%)	Solvent	Temperature (T_1,T_2)	Yield [b] (%)
1	TFA (20)	Toluene	120,80	32
2	TsOH (20)	Toluene	120,80	67
3	$LiClO_4$ (20)	Toluene	120,80	15
4	CH_3COOH (20)	Toluene	120,80	30
5	PPA (20)	Toluene	120,80	27
6	TfOH (20)	Toluene	120,80	71
7	TfOH (20)	DCE	120,80	82
8	TfOH (20)	Benzotrifluoride	120,80	70
9	TfOH (20)	CH_3CN	120,80	42
10	TfOH (20)	DMF	120,80	21
11	TfOH (20)	DMSO	120,80	18
12	TfOH (20)	Chlorobenzene	120,80	65
13	TfOH (20)	DCE	120,80	76
14	**TfOH (10)**	**DCE**	**120,80**	**88**
15	TfOH (20)	DCE	120,80	57

[a] All reactions were carried out with 0.3 mmol of 1a, 0.36 mmol of 2a,0.09 mmol aniline, 0.36 mmol I_2 in 2.0 mL of the solvent, step1 24 h and step2 12 h, unless otherwise specified.
[b] Isolated yield.

Next, we explored the amount of acid catalyst and found that it was the best relative to the raw material 10% mol.

Further, lower catalyst loading didn't achieve better yield (entry 15). Based on the above research results, the best results were obtained with α-aminoacetophenone (1.0 equiv), disulfide (1.2 equiv), aniline (0.3 equiv), and TfOH (10 mol%) in DCE as a solvent at 120 °C in step 1 for 24 h and 80 °C in step 2 for 12 h, providing the desired sulfenylindole product in 88% yield (entry 10). We also found that the yield of final sulfenylindole product was higher than indole intermediate generated in step 1, which indicated that the second-step thioetherification reaction promoted the first-step indole synthesis reaction.

With the optimization of reaction conditions, the substrate scope was then examined with various α-aminoacetophenones. As shown in Scheme 2, this reaction accommodates a broad range of α-amino-acetophenones including electron-rich or electron-deficient functional groups in any position of the aryl rings of acetophenones, yielding the products 3aa-3 am in moderate to good yields (62–94%). Further, nitro-, hydroxy-, and amino groups could not be tolerated in this trans-formation, and using amino-substituted α-.

aminoacetophenone as when starting materials, the target product cannot be detected. We next investigated the substitution effect on the aryl group of the N-aryl moiety. The electronic effect of the phenyl ring in substrate 4 had a significant effect on the yields of products. The yields of product with electron-withdrawing groups (**3ao**) were better than those of product with electron-donating groups (**3an**).

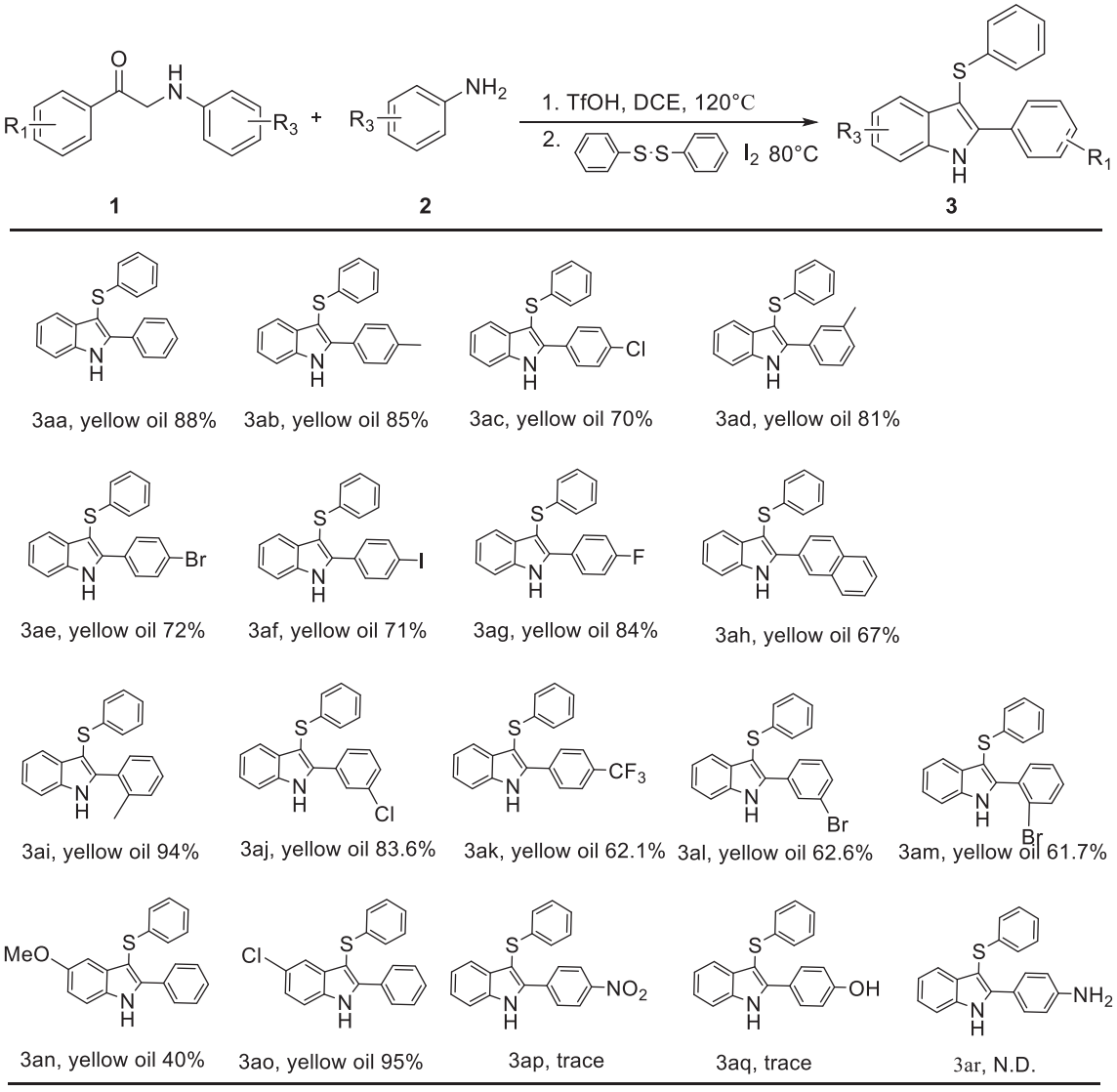
Subsequently, these reactions also using α-aminoacetophenone 1a to react with different disulfides including pyridine disulfide, methyl di-sulfide, *p*-toluene disulfide, and *p*-nitro disulfide, as shown in the Scheme 2.

Only p-chloro disulfide afforded the corresponding product 3ba in excellent yield, while *p*-methyl disulfide gave the desired products 3ea in 74% yield, which may be due to the electronic effect of the substituent in the aryl ring. Particularly, for *p*-methyl disulfide, the resulting product 3da was obtained in moderate yield, but for p-benzyl disulfide, the re-actions failed to work, and only crude mixture was generated (Scheme 3).

To gain insight into the reaction mechanism, control experiments were conducted. We used 4-methyl α-aminoacetophenone to react with 4-methylaniline (1 equiv) and aniline (1 equiv) respectively, and found that there was a competition between imine formation and Friedel-Crafts type reaction, the latter usually produces a mixture of regioisomers, but mainly target compound reacted with aniline (Scheme 4).ith aniline

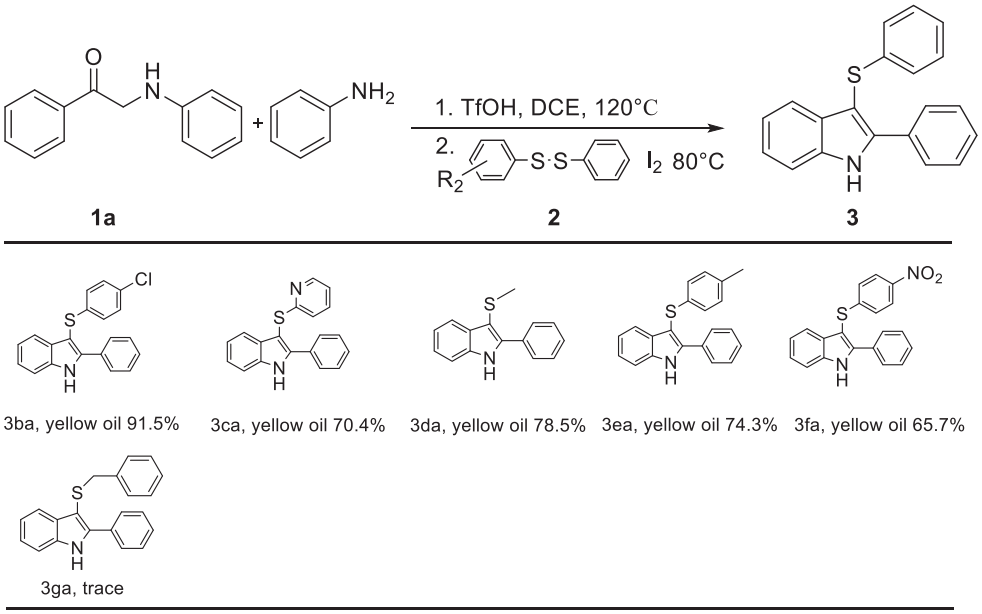
Treatment of *N*-methylacetophenone and aniline under our standard conditions afforded the desired product in 76% yield and no competitive by-product. This implies that competitive reaction can be prevented when the N—H of α-aminoacetophenone was protected, which further clarified that the N source of final product could be the external aniline.

Based on these results and the reported literature **[12,30]**, a possible reaction mechanism is proposed in Scheme 5. α-aminoacetophenone undergoes acid catalysis and undergoes electrophilic cyclization to produce 2-phenylindole after a catalytic amount of aniline starts the

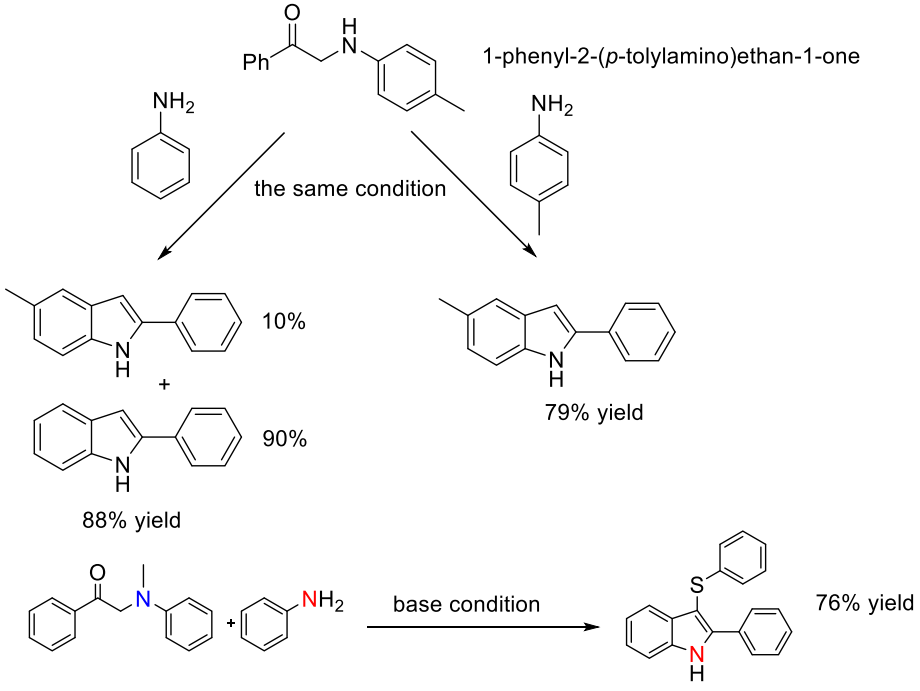


Scheme 2. TfOH-catalyzed annulation of α-aminoacetophenones [1] with sulfide (4a) [a]

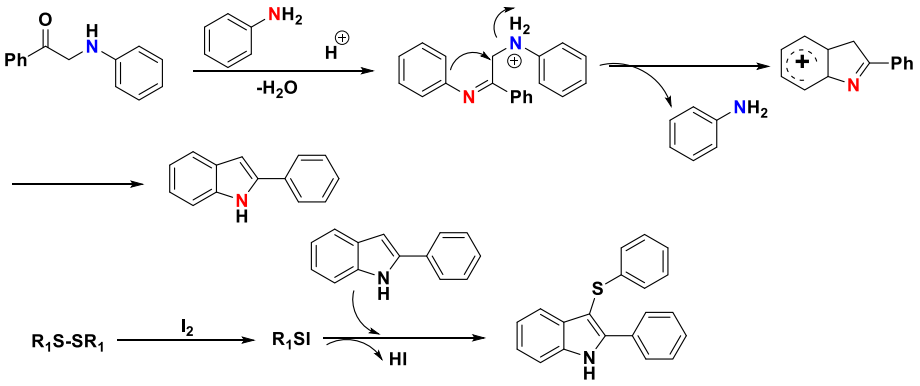
[a] Conditions: **1a** (0.3 mmol), **2** (0.36 mmol), aniline (0.09 mmol), I_2 (0.36 mmol), TfOH (10 mol%), and DCE (2 mL), step1 120 °C, 24 h, step2 80 °C, 12 h.



Scheme 3. TfOH-catalyzed annulation of α-aminoacetophenone (1a) with sulfides (2) [a].
[a] Conditions: **1a** (0.3 mmol), **2** (0.36 mmol), aniline (0.09 mmol), I_2 (0.36 mmol), TfOH (10 mol%) and DCE (2 mL), step1 120 °C, 24 h, step2 80 °C, 12 h.



Scheme 4. Mechanistic investigations



Scheme 5. Proposed mechanism for the synthesis of 3-sulfenylindoles.

reaction as a initiator. The thioether then reacts with iodine as a simple substance to obtain thionyl iodide, and 2-phenylindole then directly attacks the thionyl iodide to obtain 3-sulfide indole.

In summary, we have developed an unprecedented aniline-initiated one-pot reaction for the synthesis of highly functionalized 3-sulfenylindoles in moderate to good yields with TfOH, which is a type of green and inexpensive non-metallic catalyst.

Declaration of Competing Interest

There are no conflicts to declare.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.catcom.2020.106217.

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